REMARKS

After entry of the present amendments, claims 1-38 and 49-64 will be pending in the present application. Claims 1, 9, 36, 49, 52, and 53 are amended, new claims 59-64 are added, and claims 39-48 are canceled without prejudice. Applicants expressly reserve the right to pursue the canceled subject matter in a timely filed divisional or continuation application. No new matter is introduced by the amendment as the new and amended claim language is supported by the application as originally filed, including but not limited to, paragraphs 81-82. A complete listing of the claims as currently pending, with appropriate status identifiers included, is found on pages 3-13 of this document. Applicants respectfully request reconsideration of the present application in view of the foregoing amendments and in view of the reasons that follow.

As a preliminary matter, Applicants note that a Supplementary IDS and Form PTO/SB/08 accompany the present amendment. Applicants respectfully request that the Examiner review the listed references and return an Examiner-initialed copy of the Form PTO/SB/08 to Applicants' representative.

I. Election/Restrictions

The Office Action sets forth the restriction requirement previously imposed on the claims of the application. The Examiner divided the claims into three groups: Group I includes claims 1-38 and 49-58; Group II includes claims 39-43; and Group III includes claims 44-48. A provisional election of Group I claims was made on November 7, 2005 in a telephone conversation between the Examiner and Y. J. Suh. Applicants hereby affirm the election of Group I (i.e. claims 1-38 and 49-58), without traverse.

II. Double Patenting

Claims 1, 9, 30, 49, 52, 53, and 56-58 stand provisionally rejected over claims 3, 4, and 7-9 in copending U.S.S.N. 10/839,793 (the '793 application) for obviousness-type double patenting. As claims 3, 4, and 7-9 are no longer pending in the '793 application, there is no basis

to maintain the present provisional obviousness-type double patenting rejection. Applicants respectfully request withdrawal of the provisional rejection of claims 1, 9, 30, 49, 52, 53, and 56-58 for obviousness-type double patenting.

In the Office Action, further obviousness type double patenting issues are alleged between the pending claims and the following patents and applications: U.S. Patent Nos. 6,605,617; 6,774,237; 6,762,194; 6,800,760; and U.S. Patent Application Nos. 10/644,055 and 10/982,534. In response, Applicants respectfully point out that none of the cited patents or applications claim or disclose any methods of treatment directed to providing particular blood or plasma levels of the compounds of the present invention in a subject. Moreover, the Office Action does not identify any conflicting claims or provide any other details regarding the alleged conflicts.

In view of the lack of information regarding the alleged conflicts, Applicants respectfully draw the Examiner's attention to M.P.E.P § 804(B)(1), which states that, "any obviousness-type double patenting rejection should make clear: (A) the differences between the inventions defined by the conflicting claims...and (B) the reasons why a person of ordinary skill in the art would conclude that the invention defined in the claim at issue would have been an obvious variation of the invention defined in a claim in the patent." Given the distinct nature of the present claims with regard to particular compound levels in plasma and blood, the failure to identify specific claims of the cited patents and applications as well as reasons for the alleged conflict with the present claims, no proper obviousness-type double patenting rejections have been established for the listed patents and applications. Therefore, Applicants respectfully request that the Examiner withdraw the present rejections for obviousness-type double patenting, or comply with the requirements set forth in M.P.E.P § 804(B)(1) so that Applicants can fully respond to the rejections.

III. Claim Rejections under 35 U.S.C. § 112, 1st Paragraph

Claims 1-38 and 49-58 stand rejected under 35 U.S.C. § 112, first paragraph as allegedly lacking enablement. It is explained on page 7 of the Office Action that

> the specification, while enabling for a method of treating breast, ovarian, chronic myeloid leukemia (CML), acute myeloid leukemia (AML), multiple myeloma, colon, prostate, lung, and brain cancers in various cell lines and in an *in vivo* mouse xenograft model with the claimed quinolinone compound, does not reasonably provide enablement for treating or inhibiting the growth of all types of cancer, cancer cells, or tumors with the claimed compound. Office Action page 7.

In support of the rejection, the Examiner presents an analysis of the eight "*Wands*" factors (Office Action pages 7-10) and cites the Cecil Textbook of Medicine (21st Edition (2000), Goldman & Bennett (Eds.), W.B. Saunders Company (Pub.), Chapter 198, pp. 1060-1074). Applicants respectfully traverse this rejection. In response, Applicants respectfully submit that an analysis of the Wands factors show that the present invention as defined, e.g., by amended independent claims 1, 9, 36, 49, 52, and 53, is fully enabled throughout its scope without undue experimentation.

In view of the claims as amended, the nature of the invention and breadth of the claims have not been accurately set forth in the Office Action. Both factors support enablement without undue experimentation. For example, with respect to the nature of the invention it is asserted in the Office Action on p. 7 that the "claimed invention relates generally to chemotherapy, and specifically to compositions and methods for inhibiting the proliferation of cancer cells and tumor growth without regard to the environment (see instant claim 1) which includes both *in vitro* and *in vivo*." This assessment is incomplete and the comment on environment appears misplaced. The claimed invention relates to methods of treatment comprising exposing or administering to a subject having cancer a single benzimidazole quinolinone compound (formula I) and/or its metabolites to provide particular levels of the compound(s) in the subject's plasma or blood. The "environment" of the method—a subject—is thus clear to the skilled artisan. The

claims further recite that the cancer being treated comprises cells which express a receptor tyrosine kinase. As disclosed in the application, the compounds recited in the claims are inhibitors of receptor tyrosine kinases (see, e.g., paragraphs 10, 11, 47, and Example 3) angiogenesis (see, e.g., paragraph 47 and Example 8) and cancers expressing receptor tyrosine kinases (see, e.g., paragraphs 18, 47, 68, 82, and Examples 1, 4, and 5). Thus, the claims are not unreasonably broad, but are focused only on the types of cancers which the compounds of the invention are likely to affect – those expressing a receptor tyrosine kinase. Indeed, new claims 59-64 recite the receptor tyrosine kinase as being exactly those kinases which are shown in the working examples (i.e., Example 3) to be inhibited by the recited compounds. Accordingly, the nature of the invention is well-defined, and the claims are of reasonable breadth, being commensurate in scope with Applicants' disclosure.

Likewise, the state of the art and the level of predictability in the art as it relates to the subject matter of the amended claims further support enablement of the claimed invention. First, as shown below, the reference cited as reflecting the state of the art, the Cecil Textbook of Medicine (hereinafter, "Cecil"), is silent with regard to treating cancer with inhibitors of receptor tyrosine kinases where the cancer comprising cells expressing receptor tyrosine kinases. Second, also as shown below, it was well known at the time the present application was filed that angiogenesis is critical to the growth of cancer and is controlled by receptor tyrosine kinases, such as VEGF-RTK, and that both *in vivo* and clinical studies had validated inhibition of receptor tyrosine kinases as a powerful approach to treating cancer.

Applicants respectfully submit that Cecil, in contrast to assertions in the Office Action, fails to show the state of the art relevant to the claimed invention. Based on this reference it is asserted on page 8 of the Action that "there is no one specific chemotherapeutic agent that is effective for all types of cancer." This assertion is then pointed to in the Action as evidence of both the skill in the art, the unpredictability of the art, and the need for Applicants to demonstrate treatment of <u>all</u> cancers (pp. 8-9). Yet, despite the many agents reviewed in Cecil, receptor tyrosine kinase inhibitors, angiogenesis and vasculogenesis are note even mentioned in the

reference. Having no information whatsoever on the subject, Cecil simply is not an accurate description of the state of the art as it relates to the use of receptor tyrosine kinase inhibitors as cancer therapeutics in November 2003, when the present application was filed. Indeed, as shown below, by the time the present application was filed, inhibition of receptor tyrosine kinases for treatment of cancer was a new but accepted strategy for treating cancer.

As early as 1994, the biological relevance of the Flk-1/VEGF receptor/ligand system for angiogenesis had been investigated and demonstrated using a retrovirus encoding a dominant-negative mutant of the Flk-1/VEGF receptor to infect endothelial target cells *in vivo*. Millauer, B. *et al.*, *Nature, 367*, 576-579 (1994). Millauer, B. *et al.*, found that the growth of C6 rat glioblastoma cells was inhibited or prevented in a dose-dependent manner in nude mice infected with a recombinant retrovirus that induced the expression of the Flk-1 dominant-negative deletion mutant, LX FLK-1 TM. *Id.* at page 577 col. 1, line 39 through col. 2, line 9. On the other hand, implantation of the C6 rat glioblastoma cells in nude mice without the recombinant retrovirus produced aggressive subcutaneous tumors as shown in FIG. 2a. *Id.* Furthermore, as reported by Millauer *et al.*, and shown in FIG. 2b, even established tumors were suppressed by FLK-1 dominant-negative action. *Id.* at page 588, col. 1, lines 3-4. This demonstrated that Flk-1/VEGF function is essential for promotion of tumor angiogenesis and that blocking such function could prevent angiogenesis and inhibit tumor growth *in vivo*.

The April 2000 issue of the journal, "*The Oncologist*" was specifically devoted to presenting a diversity of preclinical and clinical studies regarding anti-VEGF strategies for cancer treatment. See Pinedo, H. M. *et al.*, *The Oncologist, 5 (Suppl. 1)*, 1-2 (2000); and McMahon, G., *The Oncologist, 5 (Suppl. 1)*, 3-10 (2000). Copies of both papers were submitted to the PTO with the IDS submitted on January 12, 2005 and acknowledged by Examiner Lewis on December 10, 2005. Excerpts from the preface to the April, 2000 volume of *The Oncologist* by Pinedo *et al.* and an article by McMahon are provided below. Together, these clearly establish that, at the time the application was filed, the importance of the role of receptor tyrosine kinases such as

VEGF in angiogenesis and tumor inhibition was significantly advanced and well understood by those skilled in the art. In particular, these articles show that:

(1) VEGF was understood to be one of the most potent and specific angiogenic factors of tumor-induced angiogenesis. Pinedo *et al.*, at page 1, col. 1, lines 11-13;

(2) VEGF was well recognized as a key factor required for tumor growth. *Id.* at page 1, col. 1, lines 15-16;

(3) Most tumors produce VEGF and inhibition of VEGF-induced angiogenesis significantly inhibits tumor growth *in vivo*. *Id.* at page 1, col. 1, lines 16-20;

(4) Inhibition of the VEGF tyrosine kinase signaling pathway blocks new blood vessel formation in growing tumors leading to stasis or regression of tumor growth. McMahon, G. *et al.*, at Abstract, lines 9-12;

(5) Tumor cells have an absolute requirement for a persistent supply of new blood vessels to nourish their growth and facilitate metastasis. *Id.* at page 3, col. 1, lines 5-7;

(6) VEGF overproduction is a major factor underlying pathological angiogenesis *in vivo* in conditions including psoriasis, macular degeneration, and tumor proliferation. *Id.* at page 3, col. 2, line 23 through page 4, col. 1, line 1;

(7) Many studies using molecular techniques provided evidence that VEGFR-2 plays an important role in tumor vascularization, growth, and metastasis. *Id.* at page 5, col. 1, lines 12-14;

(8) VEGF and its receptors were implicated in angiogenesis that occurs in numerous solid tumors including breast cancer, colon cancer, hepatoma, bladder cancer, gastric cancer, and prostate cancer. *Id.* at page 5, col. 2, lines 16-19;

(9) Compounds such as SU5416, a specific and potent inhibitor of VEGFR protein kinase and compound that inactivated Flk-1/KDR (VEGFR-2), were in clinical trials; inhibited

tumor growth *in vivo* in a dose-dependent manner; showed activity in a large number of tumor xenografts in nude mice including melanoma, glioma, fibrosarcoma and lung, epidermoid, mammary, and prostate carcinomas as well as in neuorogenic sarcoma xenografts; and produced stable disease when administered to patients with Kaposi's sarcoma and to patients with nonsmall cell lung, colorectal, and basal cell cancers. *Id* at page 6, col. 2, lines 13-30; and

(10) Compounds such as ZD4190, an orally active inhibitor of Flt-1 and Flk-1/KDR (VEGFR-2) identified by AstraZeneca, prevented VEGF-mediated proliferation of endothelial cells *in vivo* and significantly inhibited the growth of various human tumor xenografts *in vivo* including breast, colon, lung, ovarian, and prostate carcinomas. *Id.* at page 7, col. 1, lines 19-28.

Excerpts from Pinedo are presented below for the Examiner's convenience and as evidence of the high level of understanding of those skilled in the art at the time the application was filed.

> Preclinical studies have shown the major role of angiogenesis in tumor growth and metastasis formation, and therefore, inhibiting tumor angiogenesis may be a promising therapeutic modality [1, 2].
> Pinedo, H. M. *et al.*, *The Oncologist, 5 (Suppl. 1)*, 1-2 (2000) at page 1, col. 1, lines 2-6.

> Vascular endothelial growth factor (VEGF) is one of the most potent and specific angiogenic factors of tumor-induced angiogenesis [3, 4]. Originally identified for its ability to induce vascular permeability and stimulate endothelial cell growth, VEGF is now recognized as a key factor required for growth of tumors [5]. The clinical importance of VEGF for tumor growth is supported by the fact that most tumors produce VEGF and that inhibition of VEGF-induced angiogenesis significantly inhibits tumor growth *in vivo* [6-8].
> *Id.* at page 1, col. 1, lines 11-20

> VEGF expression has been shown to correlate with microvessel density in a number of solid malignancies including carcinomas of the breast, and tissue concentrations of this growth factor appear to be predictive of mortality associated with breast cancer [9, 10]. Similar results have been obtained in studies of solid malignancies in various organs including the lung, prostate, and colon [11-13]. These preclinical and clinical findings support VEGF as a promising target for anticancer

therapy.
Id. at page 1, col. 1, lines 11-20

The following excerpts are from McMahon, G., *The Oncologist, 5 (Suppl. 1)*, 3-10 (2000):

> The growth of human tumors and development of metastases depend on the de novo formation of blood vessels. The formation of new blood vessels is tightly regulated by specific growth factors that target receptor tyrosine kinases (RTKs). Vascular endothelial growth factor (VEGF) and the Flk-1/KDR RTK have been implicated as the key endothelial cell-specific factor signaling pathway required for pathological angiogenesis, including tumor neovascularization. Inhibition of the VEGF tyrosine kinase signaling pathway blocks new blood vessel formation in growing tumors, leading to stasis or regression of tumor growth. Advances in understanding the biology of angiogenesis have led to the development of several therapeutic modalities for the inhibition of the VEGF tyrosine kinase signaling pathway. A number of these modalities are under investigation in clinical studies to evaluate their potential to treat human cancers.
> McMahon, G., *The Oncologist, 5 (Suppl. 1)*, 3-10 (2000) at Abstract

> VEGF and its receptors have been implicated in the angiogenesis that occurs in many solid tumors including breast cancer [58], colon cancer [59], hepatoma [60], bladder cancer [61], gastric cancer [62], and prostate cancer [63]. Since formation of solid tumors is angiogenesis dependent, several strategies have been developed for targeting the VEGF pathway as part of anticancer therapy (Table 1) [59, 64-75].
> *Id.* at page 5, col. 2, lines 16-23

> The 3-substituted indolinone compound, SU5416, is a specific and potent catalytic inhibitor of VEGFR protein kinases [86] (Fig. 3). It inactivates Flk-1/KDR by binding in the adenine-binding pocket (Fig. 4). It is a specific VEGFR inhibitor that has virtually no inhibitory activity against serine threonine protein kinases and tyrosine kinases, such as Src, FGF receptor, Met, and Abl and has little activity against PDGF receptor [70]. At present, SU5416 is the most clinically advanced VEGF RTK-selective tyrosine kinase inhibitor being developed for antiangiogenic treatment of cancer [87]. As would be expected by its mechanism of action, SU5416 inhibits tumor growth *in vivo* in a dose-dependent manner, whereas it has no effect on tumor cells *in vitro* [70]. SU5416 has shown activity in a large number of tumor xenografts in nude mice including melanoma, glioma, fibrosarcoma, and lung, epidermoid, mammary, and prostate carcinomas [70] as well as in neurogenic sarcoma xenografts [71]. Recently, Shaheen *et al.* [59] evaluated the effect of SU5416 on tumor angiogenesis and metastasis in a human colon cancer xenograft model. In this study, SU5416 inhibited

tumor metastases, microvessel formation, and cell proliferation [59]. These findings indicate that targeting the VEGF receptor/ligand system with SU5416 decreases tumor vascularity and vessel density and increases tumor cell apoptosis and is a rational approach to inhibiting tumor growth. In a phase I clinical trial with SU5416 after enrollment of 69 patients, the drug was well tolerated at dose levels of 4.4-145 mg/m2/day, and stable disease was seen in patients with Kaposi's sarcoma and in patients with nonsmall cell lung, colorectal, and basal cell cancers [88, 89].
Id. at page 6, col. 2, line 14 through page 7, col. 1, line 9

Another substituted indolin-2-one inhibitor of RTKs, SU6668, inhibits the signaling of the VEGF receptor (Flk-1/KDR) and also targets the PDGF and fibroblast growth factor receptors [86, 90, 91]. This novel drug is believed to inhibit tumor growth by preventing angiogenesis and by its direct effects on the tumor cells and the surrounding stromal cells, which support tumor cell growth. SU6668 has recently entered phase I human trials for the treatment of solid tumors.
Id. at page 7, col. 2, lines 10-18

Several other VEGF RTK inhibitors have shown preclinical efficacy. AstraZeneca Pharmaceuticals (Macclesfield, UK) have identified a series of substituted 4-anilinoquinazolines that are potent inhibitors of VEGFR-1 and VEGFR-2. Of these, ZD4190 is an orally active inhibitor of Flt-1 and Flk-1/KDR that prevented VEGF-mediated proliferation of endothelial cells *in vitro* [72]. Following chronic oral administration, this compound significantly inhibited the growth of various human tumor xenografts *in vivo* including breast, colon, lung, ovarian, and prostate carcinomas [73]. ZD4190 has also been shown to reduce significantly vascular endothelial permeability in experimental models [74]. Two additional oral inhibitors of VEGF RTK activity, ZK222584 and CGP 41251, are under development by Novartis Pharma (Basel, Switzerland). Originally identified as an inhibitor of protein kinase C, CGP 41251 has been shown to inhibit the ligand-induced autophosphorylation of VEGF-R2/Flk-1/KDR without affecting the activity of other RTKs such as VEGF-1/Flt-1 and FGF [92]. CGP 41251 has been shown to have a broad antiproliferative effect *in vitro* and inhibits the angiogenic response to VEGF *in vivo* [92]. Similarly, ZK222584 has been shown to inhibit angiogenesis and growth of human ovarian carcinomas *in vivo* in a dose-dependent manner [75]. In mice, this compound was associated with increased survival time, decreased tumor weight, and decreased ascites volume when administered orally [75].
Id. at page 7, col. 1, line 19 through page 7, col. 2, line 16

When taken together, the articles discussed above provide irrefutable evidence that one skilled in the art understood the role of receptor tyrosine kinases in angiogenesis and cancer and the therapeutic potential of inhibitors of receptor tyrosine kinases for treating a wide spectrum of cancers.

More recent articles confirm the early results presented above and show the efficacy of using receptor tyrosine kinase inhibitors for cancer treatment. For example, a 2003 article by Beebe *et al.*, provides further evidence of the link between VEGF signaling, angiogenesis, and cancer inhibition. A copy of the Beebe *et al.* reference has been submitted with the accompanying supplementary IDS and Form PTO/SB/08. As stated in Beebe *et al.*,

> Signaling through vascular endothelial growth factor (VEGF) receptors (VEGFRs) is a key pathway initiating endothelial cell proliferation and migration resulting in angiogenesis, a requirement for human tumor growth and metastasis. Abrogation of signaling through VEGFR by a variety of approaches has been demonstrated to inhibit angiogenesis and tumor growth. Small molecule inhibitors of VEGFR tyrosine kinase have been shown to inhibit angiogenesis, inhibit tumor growth, and prevent metastases. Our goal was to discover and characterize an p.o. active VEGFR-2 small molecule inhibitor.
> Beebe *et al.*, *Cancer Research, 63*, pp. 7301-7309 (2003) at Abstract, lines 1-9

Beebe *et al.* further reports that a novel isothiazole, CP-547,632, possesses potent inhibition activity with respect to both the VEGFR-2 and basic fibroblast growth factor (FGF) kinases which, after oral administration to mice bearing NIH3T3 H-ras tumors, inhibited VEGFR-2 phosphorylation in tumors in a dose-dependent fashion (EC_{50} value of 590 ng/mL). *Id.* at Abstract, lines 9-17. As reported by Beebe *et al.*, the plasma concentration correlated well with the observed concentrations of the compound necessary to inhibit VEGF-induced corneal angiogenesis in BALB/c mice. *Id.* at Abstract, lines 17-19. The compound is reported as a potent inhibitor of both basic FGF and VEGF-induced angiogenesis *in vivo*. *Id.* at Abstract, lines 19-23. As stated by Beebe et *al.*, "The antitumor efficacy of this agent was evaluated after once daily p.o. administration to athymic mice bearing human xenografts and resulted in as much as 86% tumor growth inhibition." *Id.* at Abstract, lines 23-25. This provides further evidence that

small molecule inhibitors of VEGF-RTKs such as those set forth in the present application will retard or prevent angiogenesis and tumor growth. Thus, Beebe *et al.* confirms and extends the general understanding of the art as set forth above with respect to the articles by Pinedo *et al.* and McMahon in the April, 2000 edition of *The Oncologist*.

An article by Wedge *et al.* (Cancer Research, 62, 4645, (2002)) further shows that inhibitors of VEGF translates into inhibition of angiogenesis and inhibition of tumor growth as set forth in the April 2000 issue of *The Oncologist*. A copy of the Wedge *et al.* reference has been submitted with the accompanying supplementary IDS and Form PTO/SB/08. For example, ZD6474, [N-(4-bromo-2-fluorophenyl)-6-methoxy-7-[1-methylpiperidiny-4-yl)methoxy]quinazolin-4-amine], is a potent low molecular weight inhibitor of VEGFR-2 that translates into potent *in vitro* inhibition of VEGF-stimulated endothelial cell proliferation and provided significant antitumor activity in athymic mice implanted with a variety of histologically distinct cancers including lung, prostate, breast, ovarian, colon and vulval cancers as set forth in the following excerpt from Wedge *et al.*:

> ZD6474 [N-(4-bromo-2-fluorophenyl)-6-methoxy-7-[1-methylpiperidiny-4-yl)methoxy]quinazolin-4-amine] is a potent, p.o. active, low molecular weight inhibitor of kinase insert domain-containing receptor [KDR/vascular endothelial growth factor receptor (VEGFR-2) tyrosine kinase activity (IC_{50} = 40 nm)...The activity of ZD6474 versus KDR tyrosine kinase translates into potent inhibition of vascular endothelial growth factor-A (VEGF)-stimulated endothelial cell (human umbilical vein endothelial cell) proliferation *in vitro* (IC_{50} = 60 nM). Selective inhibition of VEGF-signaling has been demonstrated *in vivo* in a growth factor-induced hypotension model in anesthetized rat: administration of ZD6474 (2.5 mg/kg i.v.) reversed a hypotensive change induced by VEGF (by 63%) but did not significantly affect that induced by basic fibroblast growth factor. Once daily oral administration of ZD6474 to growing rats for 14 days produced a dose-dependent increase in the femoro-tibial epiphyseal growth plate zone of hypertrophy, which is consistent with inhibition of VEGF signaling and angiogenesis *in vivo*. Administration of 50 mg/kg/day ZD6474 (once-daily, p.o.) to athymic mice with intradermally implanted A549 tumor cells also inhibited tumor-induced neovascularization significantly (63% inhibition after 5 days; $P < .001$). Oral administration of ZD6474 to athymic mice bearing established (0.15-0.47) cm^3), histologically

> distinct (lung, prostrate, breast, ovarian, colon, or vulval) human tumor xenografts or after implantation of aggressive syn-geneic rodent tumors (lung, melanoma) in immunocompetent mice, produced a dose-dependent inhibition of tumor growth in all cases. Statistically significant antitumor activity was evident in each model with at least 25 mg/kg ZD6474 once daily ($P < 0.05$, one-tailed t test). Histological analysis of Calu-6 tumors treated with 50 mg/kg/day ZD6474 for 24 days showed a significant reduction (> 70%) in CD31 (endothelial cell) staining in nonnecrotic regions. ZD6474 also restrained growth of much larger (0.9 cm^3 volume) Calu-6 lung tumor xenografts and induced profound regression in established PC-3 prostrate tumor of 1.4 cm^3 volume. ZD6474 is currently in Phase I clinical development as a once-daily oral therapy in patients with advanced cancer.
> Wedge *et al.*, *Cancer Research, 62*, pp. 4645-4655 (2002) at Abstract, lines 1-37

The article further reports that ZD6474 is in Phase I clinical development as a once-daily oral therapy for the treatment of cancer. *Id.* at p. 4654.

In an article titled, "Tumor angiogenesis: past, present and the near future," Kerbel reviews the growing use of angiogenesis inhibitors in the treatment of cancer, Kerbel, R.S., *Carcinogenesis*, Vol. 21(3), pp. 505-515 (March 2000). A copy of this reference was submitted to the PTO with the IDS and Form 1449B submitted on August 8, 2005, and acknowledged by Examiner Lewis on December 10, 2005. Pages 508 and 509 of this article establish that those skilled in the art understood, at the time the application was filed, that non-solid or so-called "liquid" cancers are also angiogenesis dependent and may be treated using anti-angiogenesis drugs. An excerpt from this article follows:

> 9. The discovery of the impact of angiogenesis on `liquid' hematologic malignancies
>
> Another remarkable recent development, and one that is clearly counter-intuitive as well, is the recent realization that so-called `liquid' hematologic malignancies are angiogenesis dependent (102–104), i.e. this is not just a property of solid tumors. The discovery was based on findings such as elevated levels of pro-angiogenic growth factors, i.e. bFGF and VEGF, in the serum and urine of patients with acute lymphatic leukemia and multiple myeloma (102). Similarly, a sharp increase in bone marrow angiogenesis, as measured by means of vessel density in vascular hot spots, has also been detected in such patients (102). The newly formed blood vessels detected in the marrow of

> patients with acute lymphoytic leukemia or multiple myeloma could be a rich source of growth factors and cytokines, as well as survival factors, for tumor cells that arise in this tissue.
>
> This work has already resulted in the initiation of early phase I clinical trials to test putative anti-angiogenic drugs such as thalidomide (105) in multiple myeloma patients, the results of which look very encouraging (106). If this holds up and is found to be a consequence of an anti-angiogenic effect it would provide major impetus to a large segment of the medical oncology community to become much more actively engaged in angiogenesis research and anti-angiogenic therapies to treat these types of cancer.
> Kerbel, R.S., *Carcinogenesis*, 21(3), p. 508, col. 2, line 60 through page 509, col. 1, line 22 (March 2000)

An article by Lundberg *et al.* titled, "Bone Marrow in Polycythemia Vera, Chronic Myelocytic Leukemia, and Myelofibrosis Has an Increased Vascularity," provides further evidence that the claims are fully enabled for the treatment of non-solid cancers as well as solid cancers. Lundberg, L.G. *et al.*, *American Journal of Pathology*, Vol. 157(1), pp. 15-19 (July 2000). A copy of this reference was submitted to the PTO with the IDS and Form 1449B submitted on August 8, 2005, and acknowledged by Examiner Lewis on December 10, 2005. Excerpts from this article follow:

> Angiogenesis is a basic physiological phenomenon in many naturally occurring processes such as wound healing and embryogenesis. Its role in pathological conditions such as retinopathy in diabetes and in inflammatory conditions such as the pannus of rheumatoid arthritis has been well documented.[8] The concept of tumor induction of as well as tumor dependence on angiogenesis is widely accepted, confirming its importance in tumor growth and progression to metastatic disease.[9,10] Much of the evidence for tumor dependence on angiogenesis is based on animal studies. ...
>
> There are now a couple of studies, however, one on children with acute lymphocytic leukemia and some on adults with multiple myeloma, showing an increased vascular density in the bone marrow and elevated levels of angiogenetic peptides in serum or urine.[5,6] Another study demonstrated the increased presence of VEGF and its receptors flt-1 and KDR in the bone marrow of other hematopoietic malignancies such as myeloma.[13]
>
> We demonstrate here that the chronic myeloproliferative diseases chronic myelocytic leukemia and myelofibrosis are similarly associated

> with an increased vascular density in the bone marrow compared to the bone marrow of healthy subjects. We also observed a distinct increase in the number of cells with positive staining for VEGF in CML and a significant increase in MF versus controls, suggesting that VEGF might be an important signaling molecule for angiogenesis in these conditions. Moreover, the architecture of the vasculature clearly differs from the normal architecture in that the vessels of the three myeloproliferative disorders are more tortuous and branched. Thus, although PV did not exhibit higher microvessel density, the architecture was abnormal. This type of architecture is similar to what has been reported for various solid malignant tumors. Finally, the number of vessels and branches shows increases parallel to the general prognosis for each diagnostic entity. PV, having in general the most favorable prognosis, did not differ much from the normal marrows with respect to vessel counts and number of branches. In contrast, myelofibrosis and the case with acute myelocytic leukemia, with the shortest general life expectancy, had a significantly higher number of vessels and branches. These results can be compared to findings of increased blood flow in the bone marrow of patients with PV11 and certain abnormalities of blood vessels in relation to megakaryocytes in MF.[12]
>
> We therefore suggest that these myeloproliferative diseases, like solid tumors, may be dependent on angiogenesis to expand. The exact pathophysiological mechanisms by which this process works, as well as the diagnostic and prognostic place of this method in clinical medicine, warrant further study.
> Lundberg, L.G. *et al., American Journal of Pathology*, 157(1), p. 18, col. 1, line 21 through page 19, col. 1, line 14 (July 2000)

An article by Dankbar *et al.* titled, "Vascular endothelial growth factor and interleukin-6 in paracrine tumor-stromal cell interactions in multiple myeloma," further establishes the link between VEGF, angiogenesis and disease progression in the non-solid cancer, multiple myeloma (MM), and provides further evidence of the enablement of the claims with respect to non-solid cancers at the time the application was filed. Dankbar, B. *et al.*, *Blood*, Vol. 95(8), pp. 2630-2636 (April 15, 2000). A copy of this reference was submitted to the PTO with the IDS and Form 1449B submitted on August 8, 2005, and acknowledged by Examiner Lewis on December 10, 2005. Excerpts from this article follow:

> Interactions between myeloma cells and the bone marrow stroma, a heterogeneous compartment of various cell types and the main producer of IL-6, are well described.[15-21] Although various cytokines have been shown to mediate IL-6 secretion by myeloma-derived marrow stromal

> cells,[21-24] the involvement of angiogenic factors has not been investigated. Vascular endothelial growth factor (VEGF) is considered a potent stimulator of angiogenesis in vivo.[25] In solid tumors, VEGF expression is closely associated with the induction of neovascularization and correlates with tumor growth and metastatic potential.[26-32] In MM, marrow neoangiogenesis parallels tumor progression and correlates with poor prognosis, suggesting an angiogenesis-dependent regulation of disease activity.[33-35] In addition, VEGF expression[36,37] and angiogenic activity[38] of myeloma cells have recently been described.
>
> In the present study, we have demonstrated that VEGF165 and VEGF121 are expressed and secreted by myeloma cells and that both isoforms stimulate the expression of IL-6 by microvascular endothelial cells (MVECs) and bone marrow stromal cells (BMSCs). In turn, IL-6 stimulated the expression of both VEGF splice variants by myeloma cells, suggesting a paracrine role for VEGF in tumor-stroma interactions in MM.
> Dankbar, B., *et al.*, *Blood*, 95(8), p. 2630, col. 1, line 13 through col. 2, line 9 (April 2000)

A 1996 article by Menzel *et al.* (*Blood*, 87(3), p. 1061, col. 1, line 24 through page 1062, col. 1, line 14 (February 1996)) demonstrated that levels of bFGF were much higher in patients, especially in patients with high-risk disease, with chronic lympocytic leukemia (CLL) than in patients without the disease. Furthermore, the studies described by Menzel *et al.* indicate that bFGF contributes to the resistance of chronic lymphocytic leukemia (CLL) to apoptotic (cell death) stimulus. *Id.*, pp. 1056-1063. A copy of this reference was submitted to the PTO with the IDS and Form 1449B submitted on August 8, 2005, and acknowledged by Examiner Lewis on December 10, 2005.

Finally, a 1999 article by Gruber *et al.* (*Blood*, 94(3), p. 1082, col. 2, line 10 through page 1084, col. 1, line 18 (August 1999)) demonstrated that bFGF also plays an important role in the disease progression of patients with hairy cell leukemia (HCL). Furthermore, the article by Gruber *et al.* indicates that bFGF contributes to the resistance of HCL to chemotherapy and the survival of malignant cells similar to the results found by Menzel *et al.* with respect to CL. Gruber, G. *et al.*, *Blood*, Vol. 94(3), pp. 1077-1085 (August 1999). A copy of this reference was submitted to the PTO with the IDS and Form 1449B submitted on August 8, 2005, and acknowledged by Examiner Lewis on December 10, 2005.

Collectively, the articles show that the subject matter of the claims is not highly unpredictable as asserted in the Office Action, but is amenable to routine experimentation. In particular, the references establish that not only was the role of receptor tyrosine kinases such as VEGF-RTK and bFGFR well-known at the time the present application was filed, but this role was being exploited in the clinic with RTK inhibitors such as SU5416 and ZD6474, among others. See McMahon and Wedge. Thus, the art shows a high degree of correlation between *in vitro* results such as inhibition of receptor tyrosine kinases such as VEGF-RTK and *in vivo* anti-angiogenic and anti-cancer effects. Moreover, the fact that angiogenesis does not normally occur in adults, but is required for tumor growth and proliferation as set forth by Pinedo *et al.* and McMahon, offers a reasonable explanation to the skilled artisan as to why an angiogenesis inhibitor can act so specifically against such a wide variety of cancerous tumors. Because the present claims are precisely focused on cancers comprising cells that express receptor tyrosine kinases, the articles cited above show that the state of the art and the predictability of the art weigh in favor of enablement of the full scope of the claimed invention.

Applicants welcome the Examiner's acknowledgement on page 8 of the Office Action that "the relative skill of those in the art is high." The skilled artisan would be aware not only of Cecil, but all of the relevant art cited above which shows the accepted nature of treating cancers comprising cells expressing receptor tyrosine kinases with inhibitors of these kinases.

In view of the extensive nature of the working examples and the blood levels described for the compounds of formula I, II , and III, the amount of direction and guidance provided by the inventors clearly supports enablement of the present claims as amended. The amended claims do not recite the treatment of every cancer, but only those comprising cells expressing a receptor tyrosine kinase. As detailed below, the specification provides numerous examples and procedures for testing the recited compounds against many different receptor tyrosine kinases, many different cancer cell lines and a variety of cancer models. In particular, the working examples demonstrate the effectiveness of 4-amino-5-fluoro-3-[6-(4-methylpiperazin-1-yl)-1H-benzimidazol-2-yl]quinolin-2(1H)-one and its metabolites against a wide range of cancers.

Indeed, as acknowledged by the Examiner, the specification teaches the treatment of both solid and liquid tumors, including "breast, ovarian, chronic myeloid leukemia, acute myeloid leukemia, multiple myeloma, colon, prostate, lung, and brain cancers, in corresponding cell lines and in *in vivo* mouse xenograft models." Office Action page 9. These results directly support enablement of the claimed methods.

Applicants respectfully direct the Examiner's attention to Example 1. As shown in Table 1 (reproduced below), Example 1 details the methods for and results of testing 4-amino-5-fluoro-3-[6-(4-methylpiperazin-1-yl)-1H-benzimidazol-2-yl]quinolin-2(1H)-one against 22 cancer cell lines. The results show the extraordinary breadth of efficacy of this quinolinone against both solid and liquid tumors expressing receptor tyrosine kinases.

Table 1

$EC_{50} \leq 50$ nM	**EC_{50} 0.4- 1μM**	**EC_{50} 1-10 μM**	**$EC_{50} > 10$ μM**
MV4; 11 (AML) KM12L4a (colon cancer) HMVEC (VEGF/VEGF R2 mediated; endothelium) TF-1 (SCF/ c-KIT mediated; AML)	RS4 (ALL) 4T1 (mouse breast cancer)	MDA-MB435 (breast cancer) SKOV3 (ovarian cancer) K562 (CML) Ku812 (CML) MOLT-4 (ALL) ARH77 (multiple myeloma) HCT116 (colon cancer) Du145 (prostate cancer) PC3 (prostate cancer) H209 (lung cancer) H226 (lung cancer) HT29 (colon cancer) SW620 (colon cancer) PrC (normal prostate epithelium) HMEC (normal mammary epithelium)	U87 (brain cancer)

Example 2 identifies the two metabolites of 4-amino-5-fluoro-3-[6-(4-methylpiperazin-1-yl)-1H-benzimidazol-2-yl]quinolin-2(1H)-one recited in the claims. Table 2 discloses dose amounts of the parent compound and metabolite levels found in rat plasma.

Example 3 discloses *in vitro* testing of 4-amino-5-fluoro-3-[6-(4-methylpiperazin-1-yl)-1H-benzimidazol-2-yl]quinolin-2(1H)-one and the two metabolites identified in Example 2 in assays of a number of receptor tyrosine kinases. The receptors tested include FLT-1 (VEGFR1), VEGFR2, VEGFR3, Tie-2, PDGFRα, PDGFRβ, and FGFR1 kinases. The results, tabulated in Table 3, show that all three compounds are potent inhibitors of the all of the kinases tested and directly support enablement of the claims, especially new claims 59-64 which expressly recite these kinases.

Examples 4 and 5, show the dose response activity of 4-amino-5-fluoro-3-[6-(4-methylpiperazin-1-yl)-1H-benzimidazol-2-yl]quinolin-2(1H)-one against human colon tumor (Example 4) and human prostate cancer (Example 5) mouse xenograft models. The results are presented in Tables 4 and 7, and clearly showing the effectiveness of the compound against such cancers. In addition, the examples show the wide tissue distribution of the quinolinone.

Example 8 shows the effectiveness of 4-amino-5-fluoro-3-[6-(4-methylpiperazin-1-yl)-1H-benzimidazol-2-yl]quinolin-2(1H)-one in inhibiting angiogenesis and vasculogenesis in Matrigel mouse models, by measuring hemoglobin levels in the Matrigel plugs. The example also sets forth the actual plasma concentrations of the compound achieved at various dose levels. Thus, paragraph [0123] of the specification as originally filed states:

> Compound **1** resulted in <u>significant inhibition</u> of hemoglobin concentration in Matrigel plugs at each dose evaluated compared to plugs from vehicle treated animals (Table 8). The calculated ED_{50} was 2.6 mg/kg. The 3 and 10 mg/kg doses resulted in 54% and 57% inhibition, respectively, whereas the 30, 100, 200 and 300 mg/kg doses reduced hemoglobin to the level of unsupplemented Matrigel, resulting in 70-92% inhibition vs. FGF-supplemented controls. The plasma concentrations of compound **1** at 2 hours post dose on day 8, showed a dose proportional increase with concentrations ranging from 44 ng/mL at

> 3 mg/kg to 3920 ng/mL at 300 mg/kg (Table 9). All doses were well tolerated and no weight loss was observed. (Emphasis added.)

Example 9 illustrates metabolic profiles of 4-amino-5-fluoro-3-[6-(4-methylpiperazin-1-yl)-1H-benzimidazol-2-yl]quinolin-2(1H)-one in monkeys and shows the identification of at least one metabolite of 4-amino-5-fluoro-3-[6-(4-methylpiperazin-1-yl)-1H-benzimidazol-2-yl]quinolin-2(1H)-one. A dosing study was also performed in rats, and Table 10 of Example 9 specifically shows the blood levels of the parent compound and metabolite observed in this study.

Studies were also conducted on a number of plasma and tumor samples collected from mice, as illustrated in Example 10. Paragraph [0130] summarizes the results:

> Significant activity was observed *in vivo* in the HCT116 human colon tumor model. In HCT116 tumors, compound **1** inhibited the phosphorylation of ERK (MAPK) in a dose- and time-dependent manner and significant changes in histology analyses of the tumors was observed. (Emphasis added.)

Example 11, further illustrates the extent to which 4-amino-5-fluoro-3-[6-(4-methylpiperazin-1-yl)-1H-benzimidazol-2-yl]quinolin-2(1H)-one and its metabolite pervade tissue after administration. Example 11 illustrates this through the use of radio-labeled 4-amino-5-fluoro-3-[6-(4-methylpiperazin-1-yl)-1H-benzimidazol-2-yl]quinolin-2(1H)-one, with the results partially summarized in paragraph [0133] of the specification:

> Following oral administration of ^{14}C-**1**, radioactivity derived from ^{14}C-**1** was widely distributed throughout all tissues by 1 hour postdose, and had reached C_{max} in most tissues by 4 hours postdose. Overall distribution of radioactivity in the tissues of males and females was similar. ^{14}C-**1**-derived radioactivity was cleared more slowly from tissues than from plasma. In males and females, the highest tissue concentrations of ^{14}C-**1**, excluding the gastrointestinal tract through 24 hours were detected in the harderian gland, adrenal gland, renal medulla, intra-orbital lacrimal gland, and exorbital lacrimal gland. ^{14}C-**1**-derived radioacitivity crossed the blood/brain barrier after oral dose administration.

Examples 8-11 thus also provide extensive evidence of blood and tissue levels of the compound of formula I.

The quantity of experimentation needed to make or use the invention based on the content of the disclosure is reasonable. Applicants respectfully draw the Examiner's attention to the discussion of the undue experimentation factors (Wands factors) in the M.P.E.P., which states that the "fact that experimentation may be complex does not necessarily make it undue, if the art typically engages in such experimentation." (§ 2164.01, emphasis added.) Because the claims as amended are directed to methods involving cancers comprising cells expressing receptor tyrosine kinases, and all of the extensive working examples and guidance provided throughout the specification are directed to exactly these types of cancer, the quantity of experimentation necessary to practice the skilled artisan is typical and, therefore, routine. In view of the articles cited above and the procedures and guidance provided by Applicants' disclosure, the skilled artisan is well aware of which cancers are known to comprise cells expressing a receptor tyrosine kinase and how to identify whether any particular cancer comprises such kinases. Consistent with this statement, Applicants note that the compound of formula I is presently undergoing Phase II clinical trials for the treatment of cancer.

Taken as a whole, the working examples in conjunction with the rest of the specification provide ample guidance and direction to enable one of skill in the art to practice the invention without anything more than routine experimentation. As pointed out in the M.P.E.P. § 2164.01(a), the mere "fact that experimentation may be complex, does not make it undue if the art typically engages in such experimentation." Given the small number of compounds recited in the methods, the understanding by skilled artisans of the link between the inhibition of receptor tyrosine kinases and the inhibition of angiogenesis and cancer as demonstrated by numerous journal articles, The high level of skill in the art, the extensive disclosure of actual procedures and test results, and the guidance provided in the application, Applicants respectfully submit that the quantity of experimentation required by the skilled artisan to practice the claimed invention is

routine. Accordingly, Applicants submit that the full scope of the claims is enabled and request that the Examiner reconsider and remove the rejections under 35 U.S.C. § 112, first paragraph.

Applicants believe that the present application is now in condition for allowance. Favorable reconsideration of the application as amended is respectfully requested. If any issues remain to be resolved in view of this amendment and reply, the Examiner is invited to contact the undersigned by telephone to achieve a prompt disposition thereof.

Please direct all correspondence to the attorney or agent at the **correspondence address** indicated below with Customer Number **27476**.

Respectfully submitted,

Date August 17, 2006

By _____

Joseph P. Meara
Attorney for Applicant
Registration No. 44,932

FOLEY & LARDNER LLP
Customer Number: 23524
Telephone: (608) 258-4303
Facsimile: (608) 258-4258

Correspondence Address:

NOVARTIS VACCINES AND
DIAGNOSTICS, INC.
Customer Number: 27476
Attorney Y. J. Suh
Reg. No. 41,337
Novartis Vaccines and Diagnostics, Inc.
Intellectual Property-R440
P.O. Box 8097
Emeryville, CA 94662-8097
Telephone: (510) 923-2706
Facsimile: (510) 655-3542